

## New vaccine adjuvants – MPL paves the way

**LONDON, UK----20<sup>th</sup> October 2009----ExpertREACT.** The FDA's decision to approve GSK Biological's Cervarix<sup>®</sup> is not only a step forward for human papilloma virus (HPV) disease prevention; it is a step forward for the whole vaccine industry. With FDA policy towards new adjuvants now evolving, **VacZine Analytics** believes the industry will now elevate investment in the field. Once again the H1N1 pandemic is a catalyst.

On the 16<sup>th</sup> October, GSK announced that the US FDA had approved its bivalent HPV vaccine Cervarix<sup>®</sup> (1). Cervarix<sup>®</sup>, although being approved in 100 countries around the world, and gaining WHO prequalification, had experienced delays in getting US approval after receiving a complete response letter in December 2007 and submitting final requested data in March 2009. Data studied by the FDA involved trials of the vaccine in 30,000 girls in 20 countries. Also Cervarix<sup>®</sup> has recorded significant "real use" being now part of large national immunization programs such as in the UK, where around one million girls have been vaccinated so far (2).

Among other things, many believed part of the reason for the FDA's hesitancy with Cervarix<sup>®</sup> was the fact the vaccine contained a new vaccine adjuvant, 3-O-desacyl-4'-monophosphoryl lipid A (MPL). The FDA is well known to be "ultra" conservative due to vaccine safety concerns. Note: the withdrawal of Wyeth's Rotashield in 1999 (rotavirus vaccine) due to fatal intussusception of the bowel after launch one year earlier (3). Another often cited, and now extremely relevant example, is the Guillain Barre Syndrome (GBS) connection with the 1976 "swine flu" vaccination program. Until this recent news, the only vaccine adjuvant approved in the US market was alum, which had been discovered at the beginning of the century. Note that Merck & Co's HPV vaccine, Gardasil which was approved back in 2006, is a traditional alum containing vaccine.

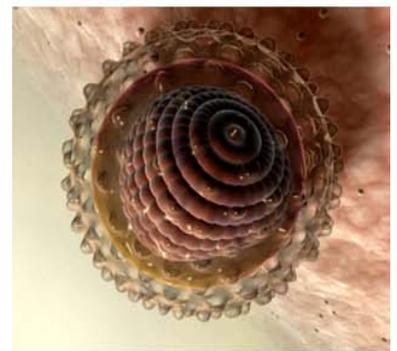
Vaccine adjuvants are powerful stimulators of the immune system and therefore do raise safety concerns. Cervarix<sup>®</sup>, itself has not been without controversy, especially in the UK where a 14 yr girl died shortly after receiving the vaccine (2). Although the vaccine has not been linked to the death, in the public mind the connection tends to remain prolonged. There have also been other instances of vaccines containing new adjuvants having safety concerns, especially within clinical trials. Note the example of Merck & Co's Hepsilav (HBV vaccine) and Wegener's granulomatosis in a Phase III study. Hepsilav contained immunostimulatory DNA sequences and only recently has been removed from a FDA clinical hold (September 2009).

The vaccine industry has pursued the development of new adjuvants, mostly due to scientific but ultimately commercial reasons. From an immunologist's perspective, alum as an adjuvant is limited. It preferentially stimulates humoral antibody specific responses known as Th2 type, which are suitable for protection against some diseases e.g. influenza. However, in other diseases which involve complex latent pathogens e.g. TB, HSV, HIV and malaria, a more complex immune response is required for vaccine effect. Often this requires stimulation of other parts of the immune system such as cell mediated responses (CMI) or Th1 responses.

GSK's MPL is known to have a Th1 bias and therefore opens many possibilities for the company who are keen to promote the benefits of new adjuvants to the investment community (4). For GSK's licensed products, while MPL's inclusion in Cervarix<sup>®</sup> is touted as inducing a broader and more lasting response, the H1N1 pandemic vaccine, Pandemrix<sup>™</sup> has allowed the company to strengthen the "dose sparing" argument for MPL. Recent data indicates that in 100% of subjects receiving Pandemrix<sup>™</sup> (3.75 mcg), antibody titres exceeded regulatory threshold of 1:40 seroprotection after the first dose 3 weeks following vaccination (5). The vaccine was more immunogenic than an unadjuvanted vaccine comparator.

Out of all the major players, GSK has invested the most in novel adjuvants with at last count around 60% of its R&D pipeline containing an MPL system (6). Some observers have perceived this to be a high risk approach should an issue be linked with MPL, but with the FDA approval of Cervarix<sup>®</sup>, GSK's approach may finally pay off. Other vaccine companies have made notable investment in novel vaccine adjuvants mainly by acquisition: Pfizer (Coley) and Merck & Co (Idera) or in-license: Wyeth and Sanofi Pasteur (IC31, Intercell AG). Novartis Vaccines continue to push forward their MF-59 adjuvant which is still not US-approved.

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It is reasonable to assume that with the FDA approval of Cervarix<sup>®</sup>, the US regulatory stance may become more amenable to new adjuvant technologies. Obviously this evolution in policy must be coupled with more investment in basic scientific research focused on understanding the exact mechanism of action for many new adjuvants and downstream safety implications.

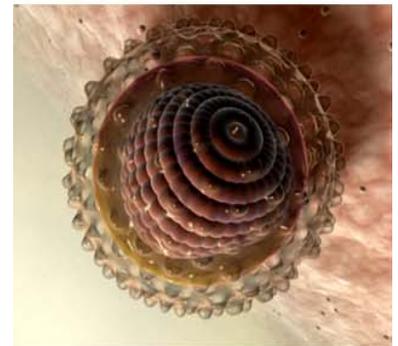
As more and more companies experiment with the idea of therapeutic vaccination for cancer and chronic disorders, their confidence to invest further will be heightened with this recent news. Complex methods of immunomodulation are necessary to these vaccine approaches and require novel adjuvants. Finally, one cannot help but think that the ongoing H1N1 pandemic, and possibility of limited vaccine supplies in the US, has supported the US case for MPL which in the EU and Rest of World region has been approved for some time now.

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**References and Notes:**

*\*Major Western markets are considered United States, United Kingdom, France, Germany, Italy and Spain*

- 1) GSK Corporate Press Release. October 2009. Available at: [http://www.gsk.com/media/pressreleases/2009/2009\\_pressrelease\\_10112.htm](http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10112.htm). Accessed October 2009.
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- 4) GSK Investors Presentation. Delivering a unique vaccines pipeline. September 2009. Available at: <http://www.gsk.com/investors/presentations/2009/Thomas-Breuer-28September2009.pdf>. Accessed October 2009.
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- 6) Vaccine R&D Pipeline Database, September 2009. Register for free access on-line at <http://www.vaccinestats.com>. Published by **VacZine Analytics**.



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